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Pharmacovigilance Skills, Knowledge and Attitudes in our Future Doctors – A Nationwide Study in the Netherlands

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Abstract: Pharmacovigilance centres monitor the safety of drugs, based on adverse drug reactions (ADRs) reported by doctors, pharmacists and pharmaceutical companies. However, the under-reporting of ADRs remains a major problem. Our aim was to investigate preparedness of future doctors for their role in pharmacovigilance, by assessing their pharmacovigilance awareness, skills and knowledge. The study was a nationwide e-survey among medical students (third to sixth year) of all eight medical schools in the Netherlands. The survey consisted of questions regarding pharmacovigilance awareness, skills and knowledge. Overall, 874 students provided informed consent and participated (response 12%). Almost all students (96%) intended to report serious ADRs in their future practice. Almost half (44%) of the students did not know where to report an ADR, and 78% did not know which items were necessary for a good-quality ADR report. While more than 78% of the students agreed that pharmacovigilance is an important topic in their medical education, only 26% found that their current curriculum covered pharmacovigilance adequately. Although ADR reporting is considered relevant and important among future doctors, many do not know where and what to report. This is highly undesirable and should have consequences for pharmacotherapy teaching.

Pharmacovigilance centres have a vital function in safeguarding patient safety and the appropriate use of medicines worldwide, by monitoring the adverse drug reactions (ADRs) of pharmaceutical products that have been given marketing approval. Monitoring is essential to identify undetected, uncommon and serious ADRs and to thereby improve medication safety and the understanding of drug risks [1–3]. The spontaneous reporting of ADRs to pharmacovigilance centres is a common and inexpensive method of ADR detection in many countries [3], which makes centres dependent on the quality and quantity of these spontaneous ADR reports. Despite the recognized importance of post-marketing surveillance, under-reporting remains a barrier for optimal ADR monitoring [2,4,5]. Most ADRs are reported by health professionals [4,6,7], and in many countries, among which the Netherlands, the reporting of serious or previously unrecognized ADRs is mandatory. In some European countries, such as Sweden, the Netherlands and Portugal, patients can also

report ADRs, and in the Netherlands, even medical and pharmacy students can report ADRs to the Netherlands Pharmacovigilance Centre Lareb [8–12].

The legal obligation to report ADRs requires health professionals to have the knowledge and skills to recognize and adequately report these reactions. During their medical training, medical students are typically taught how to prescribe rationally on the basis of the WHO Guide to Good Prescribing [13–15], and the last step of the six-step method covers the follow-up of prescribing; however, it is not known whether medical students are adequately prepared for their role in monitoring and reporting ADRs. Previous studies have shown that pharmacy students have insufficient knowledge of pharmacovigilance and ADR reporting [1,16]. We expected a similar insufficient preparedness among medical students, and by identifying the nature of this insufficiency, we would be able to improve future (medical) pharmacovigilance education. Therefore, the primary objective of this study was to investigate whether medical students are sufficiently prepared for their role in pharmacovigilance. A secondary objective was to evaluate the intention/attitudes and skills/knowledge of these students towards pharmacovigilance and ADR reporting.

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Methods

Setting. This national, anonymous, cross-sectional study was carried out on behalf of the working group 'Pharmacotherapy Education Research' of the Dutch Society for Clinical Pharmacology & Biopharmacy (NVKF&B), in collaboration with the Netherlands Pharmacovigilance Centre Lareb (Lareb). The pharmacotherapy education co-ordinators of the eight medical schools in the Netherlands were invited to participate in this project. These co-ordinators regularly attend meetings of the education subcommittee of the NVKF&B to improve clinical pharmacology and pharmacotherapy teaching [17]. The STROBE guidelines were followed where possible [18].

Population. All students were invited by their medical school to voluntarily complete an anonymous e-survey. We aimed to include only third- to sixth-year medical students, as these students would shortly start clinical practice, either as junior doctor or during clerkships. We expected a response rate of 10–25%.

Instrument. The e-questionnaire started with an information letter and informed consent statement and consisted of 10 questions (with some questions consisting of multiple statements). If a question was answered, it was not possible for respondents to return to earlier answers (since some questions consisted of the answers on earlier answered questions). There was no time limit for e-questionnaire completion, but on the basis of a pilot study we estimated that it would take 5–6 min. to complete the questionnaire. In this pilot study, we also tested the face validity of the e-questionnaire in final-year students who were not participating in the current study. Besides participant characteristics (*sex, study year, university*), the survey consisted of the following three themes.

Knowledge and skills. Knowledge and skills regarding pharmacovigilance and ADR reporting were investigated using an open-ended question and dichotomous questions. The open-ended question was as follows: 'If you think that a patient is having an adverse drug reaction, what would you do?' In four merged dichotomous contingency questions (no/yes, specify your answer (open-ended)), we investigated whether students knew where, how and why to report ADRs and if they had reported an ADR before. For example, if a participant answered 'yes' to the following question 'I know where I can report adverse drug reactions (in the Netherlands)', he/she would be asked to specify where they should make this report (the Netherlands Pharmacovigilance centre Lareb). There were also 12 closed-ended dichotomous questions (yes/no). Of those, 9 questions had been used in an earlier survey for pharmacists and pharmacy students and had been adapted for medical students [6,16,19].

Intention / Attitudes. Intention and attitudes towards pharmacovigilance/ADR reporting were evaluated using three questions. The first question consisted of five statements on the intention to report ADRs, three of which had been used earlier in the survey of pharmacists and pharmacy students [6]. The other two statements investigated the probability of the participant reporting an ADR, dependent on the severity of the ADR and the participant's familiarity with the reaction. The second question probed opinions and beliefs regarding ADR reporting and pharmacovigilance, using a number of statements. Many of these statements are used during pharmacovigilance teaching (see separate heading) and had been adapted for medical students [1]. These statements were scored on a 5-point Likert scale (1: strongly disagree to 5: strongly agree). The third question included eight statements on what students would expect to be the likely outcome of reporting ADRs (7-point Likert

scale; 1: extremely unlikely to 7: extremely likely). The first seven statements had been adapted from the study of Gavaza [16].

Student opinion of current pharmacovigilance teaching. The third and last part of the survey covered students' opinions of their current and past education in pharmacovigilance, whether they considered this education sufficient and appropriate for future clinical practice. Some of the statements had been used previously and had been adapted for medical students [1]. Answers were given on a 5-point Likert scale (1: strongly disagree to 5: strongly agree). The participants were also asked how they would prefer to be taught about pharmacovigilance and ADRs.

Data analysis. All data were imported in SPSS Statistics 22 (IBM Corp. Armonk, NY, USA). Descriptive statistics were used to report frequencies and means/standard deviations (S.D.) of survey results. Open questions were analysed using content analysis/thematic analysis [20]. The mean aggregate intention score was calculated as the sum of the original three intention statements [6]. The mean composite knowledge score was calculated as the sum of the correct answers divided by the number of answered questions (uncorrected for guessing). Skills were analysed as two separate variable (i.e. knowing where to report and knowing what to report). Reliability of the composite intention was tested using Cronbach's α . A one-way ANOVA was used to compare the mean intention scores and composite variable (intention, knowledge and skill scores) with baseline characteristics (study year, medical school (anonymized)). If the ANOVA tests revealed significant differences within a group, *post hoc* tests were used to differentiate between subgroups. The Gabriel's *post hoc* test was used when sample sizes of these subgroups were slightly different [21]. A significance level ($p \leq 0.05$) was considered statistically significant for all analyses.

Ethical considerations. This study did not fall under the scope of the Dutch Medical Research Involving Human Subjects Act (WMO). Participation was voluntary and anonymous, and all participants were informed and gave informed consent based on an information letter. Furthermore, the ethics review board of the Netherlands Association for Medical Education (NVMO) reviewed and approved this research (protocol) (ID: 440).

Results

In total, 874 students from the eight medical schools provided informed consent and participated (baseline characteristics are displayed in Table S1). Response rates varied between medical schools and study year (mean 12%, range 7–24%). Of the 858 students who provided information about their study year, 354 were in their third year of medical school, 92 in their fourth year, 106 in their fifth year and 298 in their sixth year. Most (73%) of the participants were women and only 84 (10%) had reported one or more ADRs before (range 1–5 reports); most of these students ($n = 57$, 68%) were from 'Medical school 1'. Almost all sixth-year medical students (94%) from 'Medical school 1' had reported an ADR before, which was expected given the mandatory ADR reporting instruction in that medical school's curriculum [9,12].

Knowledge and skills.

If the respondents detected an ADR in the future, most (70%) would search for additional information (i.e. in the literature,

take an extended history from their patient or suggest additional diagnostics) about that ADR. Almost half (47%) would search for an alternative drug, 33% would withdraw the suspect drug, and 21% would ask help/advice from their supervisor or the hospital pharmacist. The action students took would depend on the severity of the ADR (22%), and 16% indicated they would report the ADR, either to some authority (i.e. in general 'I would report the ADR somewhere' or specifically 'Report the ADR to Lareb'). The number of sixth-year medical students who would report an ADR was only slightly higher than that of students in other years (ANOVA $p = 0.221$), being 18% (see how students would respond to an ADR in Table S2).

Overall, 65% of the third-year and 22% of sixth-year students did not know where they should report an ADR (one-way ANOVA, $p < 0.001$, see fig. 1). However, more students from 'Medical school 1' knew where they should report an ADR compared with students from the other medical schools (75% versus 31–53% in the other medical schools; one-way ANOVA, Gabriel *post hoc*, $p < 0.001$ to $p = 0.027$). Of the students who knew where they should report ADRs ($n = 419$), 93% mentioned Lareb and 8% mentioned that they would use Internet to find out where they should report the ADR or would report to another institution, such as the Dutch Drug Formulary (Farmacotherapeutisch Kompas, 4%) (see Table S3).

Almost none (90%) of the third-year medical students and 66% of the sixth-year students did not know which items were necessary for a good ADR report (one-way ANOVA, $p < 0.001$, see fig. 1). Students from 'Medical school 1' scored significantly better (47.3%) than students attending the other medical schools (range 81–88%, ANOVA, Gabriel *post hoc*, all $p < 0.001$). The items the students mentioned as necessary for a good ADR report are displayed in Table S4.

The mean score for the 12 dichotomous knowledge questions was 66% (not corrected for guessing; see table 1). Scores

differed significantly between study years but not between medical schools (one-way ANOVA, $p = 0.008$ and $p = 0.371$, respectively). In general, the sixth-year students scored marginally better (mean 68% S.D. = 14.2) than the third-year medical students (mean 64% S.D. = 14.7) (one-way ANOVA, Gabriel *post hoc*, $p = 0.005$). Students had the least knowledge about which ADR should be reported to the Pharmacovigilance Centre Lareb. Less than half of the students were aware that patients and/or medical students could report ADRs (even during their clerkships).

Intention and attitudes.

Almost all students intended to report future ADRs to Pharmacovigilance Centre Lareb in different situations (see table 2). The aggregate Intention score was reliable (Cronbach's $\alpha = 0.918$), and on average 18.27 (S.D. = 2.74), not influenced by study year or medical school (one-way ANOVA, $p = 0.234$ and $p = 0.266$, respectively). Students who had reported an ADR earlier had a higher score (mean 18.86, S.D. = 1.92) than the students who had not reported an ADR earlier (mean 18.20 S.D. = 2.82) (one-way ANOVA, $p = 0.040$). In the eight statements on what students expected to be the likely outcome of reporting an ADR, they agreed to favourable outcomes ('Contribute to the safe use of medicines' and 'Improve patient safety'). They did not anticipate that reporting would 'Disrupt the normal workflow' or be 'Time-consuming'. The latter two were scored similarly by students who had or had not previously reported an ADR (one-way ANOVA $p = 0.455$ and $p = 0.303$, respectively).

Student opinion about current pharmacovigilance teaching.

Opinions and beliefs about ADR reporting and pharmacovigilance were adapted to medical instead of pharmacy students [1] and are reported in table 2. Overall, 79% of the students agreed that pharmacovigilance should be an important component of medical education, but only 26% agreed that their current curriculum covered pharmacovigilance well. Only 48% of the sixth-year medical students felt sufficiently prepared to report ADRs in future practice. When asked how they would prefer to learn about pharmacovigilance and ADRs, the majority (76%) indicated they would prefer a practical assignment (e.g. making an ADR report).

Discussion

Although ADR reporting is considered relevant and important by future doctors, many medical students who will shortly enter practice did not know what to do, and where and what to report. Even though there is international recognition of the importance of pharmacovigilance and ADR reporting, this has not been accompanied by emphasis on ADR reporting in clinical or teaching practice. This is highly undesirable and efforts should be taken to improve pharmacovigilance skills and knowledge among medical students.

We found that medical students did not know how to act if they were to encounter an ADR in clinical practice – most

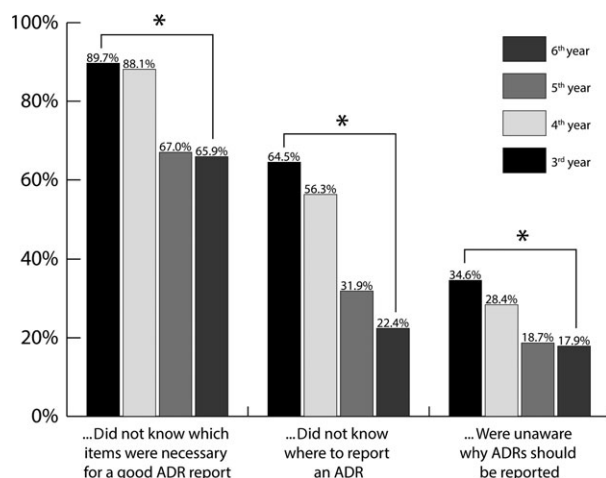


Fig. 1. Skills and knowledge of reporting adverse drug reactions and pharmacovigilance among medical students in the Netherlands in different study years. Statistical significant differences are indicated with an asterisk (*).

Table 1.

Knowledge/skills regarding the reporting of adverse drug reactions of medical students in different study years, *correct answer, displayed % is % of students with Correct Answer.

	3rd year	4th year	5th year	6th year	Total
1. All ADRs, irrespective of severity, must be reported (*No)	41.6%	35.4%	41.4%	56.9%	46.7%
2. Doctors should report serious ADEs even if uncertain that product caused the event (*Yes)	85.1%	87.7%	85.1%	83.9%	84.9%
3. Doctors should report serious ADEs even if do not have all details of event (*Yes)	80.1%	90.8%	75.9%	86.7%	83.0%
4. All serious ADRs are known before a drug is marketed (*No)	84.0%	90.8%	93.1%	91.4%	88.5%
5. Lareb does not disclose ADR reporter's identity (*Yes)	86.5%	87.7%	83.9%	81.2%	84.3%
6. One can report ADEs anonymously to Lareb (*Yes)	81.9%	84.6%	81.6%	76.5%	80.1%
7. Adverse experiences with cosmetics and special nutritional products may be reported to Lareb (*Yes)	38.1%	33.8%	32.2%	29.8%	33.9%
8. Adverse experiences with natural or homeopathic products may be reported to Lareb (*Yes)	52.3%	47.7%	57.5%	52.9%	52.8%
9. Adverse experiences with vaccines may be reported to Lareb (*Yes)	94.3%	100.0%	98.9%	95.7%	95.9%
10. One case reported by a doctor does not contribute much to knowledge on drug risks (*No)	65.8%	70.8%	73.6%	72.9%	69.9%
11. I have adequate knowledge of ADE reporting (*Yes)	16.0%	13.8%	40.2%	40.8%	28.1%
12. Patients can report ADRs independent from a healthcare professional (*Yes)	46.3%	49.2%	48.3%	52.5%	49.1%
Total 12 knowledge questions	64.3%	66.0%	67.6%	68.4%	66.4%

would only look for more information or perform additional tests. The emphasis on diagnostic testing instead of action and (pharmaco)therapeutics is a notorious problem in medical pharmacotherapy education [22,23]. Furthermore, only a small minority of students spontaneously mentioned reporting an ADR, similar to the estimated extent of under-reporting among doctors [4]. Unexpectedly, a substantial proportion of sixth-year medical students did not know to which authority they should report ADRs. Although students' skills and knowledge about reporting seemed inadequate, they did recognize the importance of ADR reporting, which we considered positive.

A previous literature review identified multiple factors as underlying the low level of ADR reporting: indifference, lethargy (including lack of motivation and time) and negative expectations of the result of reporting were the most cited reasons not to report [24]. As opposed to these findings, we found students to have favourable intentions and attitudes regarding ADR reporting. Almost all students intended to report serious ADRs in the future. Moreover, with the same questionnaire, medical students had higher scores than pharmacists and pharmacy students [6,16]. Students who had reported an ADR before expressed the intention to report serious ADRs in the future more often than students who had not previously reported an ADR.

The results of this study, regarding the limited proficiency in pharmacovigilance skills and knowledge among medical students, can probably be generalized to medical schools in other countries. The Netherlands has a long tradition in pharmacovigilance and pharmacotherapy teaching and has been an example for other (European) countries. Problem-based pharmacotherapy teaching based on the WHO six-step method has been implemented in the curricula of all medical schools in the Netherlands [17,25]. The study had a number of strong points, such as the inclusion of a large number of students in the third to sixth year of medical training, the use of validated questionnaires on ADR reporting knowledge and attitudes, enabled us to compare the attitude and knowledge of (future) health professionals, and the inclusion of open-

ended questionnaires provided information about how students would currently respond to ADRs [1,6,16]. However, a limitation of this study is self-selection bias, as students voluntarily and anonymously participated. The volunteers are probably the ones most interested/concerned with the topic of pharmacovigilance and would plausibly do better compared to the less interested (non-responders). Our results might therefore be an overestimation of the knowledge and attitude to ADR reporting of medical students in general. The response rate of 12% may be perceived as a limitation; however, still 874 students from all medical schools in the Netherlands participated. Despite these shortcomings, the study contributes to our knowledge of how students would report ADRs and identified gaps in their knowledge of how, when and where to report such events. This knowledge should be harnessed to improve the pharmacovigilance of medical students and doctors.

The results for one of the medical schools were probably influenced by a pilot project on ADR reporting run by Lareb. Students from this medical school performed better regarding where and what to report to the national pharmacovigilance centre. Although results were promising, pharmacovigilance should be further improved, by incorporating a (mandatory) ADR reporting assignment in the medical curriculum. In collaboration with Lareb, an educational package consisting of (digital) casuistry, a lecture and an ADR assignment has been developed and is available to Dutch medical schools [9]. Various efforts have been suggested to stimulate ADR Reporting such as integrating a 'ADR report link' in an electronic medical record or using an app. Although these suggestions seem promising, reporting ADRs still depends on the awareness and skills of the (future) doctor. Another initiative that could further improve pharmacovigilance awareness, knowledge and skills is the student-led assessment of ADR reports as practised in the VUmc Learner centred student-run clinic project, which is run in collaboration with the Netherlands Pharmacovigilance Centre Lareb [26,27]. Further research is needed to determine the feasibility and effects of these novel

Table 2.

Intention, attitudes and opinions regarding the reporting of adverse drug reactions and pharmacovigilance (education) among medical students in the Netherlands.

	N	Mean (S.D.)	1- Extremely unlikely	2	3	4 - Neither likely nor unlikely	5	6	7 - Extremely likely
Could you indicate how likely it is you will report an ADR to Lareb in the following situations:									
(General) I plan to report ADRs that I will encounter	716	4.95 (1.23)	0.6% (4)	3.1% (22)	8.8% (63)	18.6% (133)	35.6% (255)	24.6% (176)	8.8% (63)
I plan to report unknown (to me) ADRs that I encounter	716	5.59 (1.11)	0.6% (4)	1.1% (8)	3.5% (25)	6.8% (49)	29.7% (213)	38.4% (275)	19.8% (142)
I intend to report serious ADRs that I encounter	716	6.17 (0.95)	0.7% (5)	0.4% (3)	0.4% (3)	2.2% (16)	13.5% (97)	41.1% (294)	41.6% (298)
I will try to report serious ADRs that I encounter	716	6.10 (1.00)	0.8% (6)	0.4% (3)	1.0% (7)	3.1% (22)	13.7% (98)	42.3% (303)	38.7% (277)
I plan to report serious ADRs that I encounter	716	6.00 (1.01)	0.7% (5)	0.3% (2)	0.7% (5)	5.6% (40)	16.5% (118)	41.6% (298)	34.6% (248)
Mean aggregate intention score	716	18.27 (2.74)							
How likely do you think the following outcomes will be if you report a serious ADR:									
Educates others about drug risks	674	5.83 (0.99)	0.6% (4)	0.7% (5)	1.3% (9)	3.6% (24)	23.7% (160)	46.1% (311)	23.9% (161)
Personally beneficial	674	3.81 (1.55)	7.0% (47)	16.3% (110)	17.5% (118)	27.0% (182)	16.2% (109)	12.6% (85)	3.4% (23)
Improves patient safety	674	6.06 (0.91)	0.4% (3)	0.6% (4)	0.7% (5)	1.6% (11)	16.8% (113)	46.7% (315)	33.1% (223)
Increases risk of malpractice	674	2.84 (1.32)	16.3% (110)	27.4% (185)	26.7% (180)	20.6% (139)	4.6% (31)	3.3% (22)	1.0% (7)
Breaks trust with patients	674	2.32 (1.12)	23.4% (158)	38.7% (261)	27.9% (188)	5.8% (39)	1.8% (12)	1.6% (11)	0.7% (5)
Disrupts the normal workflow	674	4.09 (1.52)	4.9% (33)	11.7% (79)	17.7% (119)	22.8% (154)	26.7% (180)	10.1% (68)	6.1% (41)
Time-consuming to report	674	4.27 (1.16)	1.6% (11)	4.6% (31)	12.5% (84)	45.3% (305)	21.4% (144)	11.4% (77)	3.3% (22)
Contributes to the safe use of medicines	674	6.06 (0.96)	0.7% (5)	0.6% (4)	0.3% (2)	2.1% (14)	18.0% (121)	43.5% (293)	34.9% (235)
	N	Mean (S.D.)	Completely disagree	Disagree	Neutral	Agree	Completely agree		
Opinion regarding (current) education in pharmacovigilance									
Pharmacovigilance should be included as a core topic in medical education	724	3.87 (0.70)	0.4% (3)	4.3% (31)	16.7% (121)	65.3% (473)	13.3% (96)		
Pharmacovigilance is well covered (up to now) in my medical school curriculum	724	2.75 (0.99)	8.8% (64)	35.6% (258)	29.3% (212)	24.0% (174)	2.2% (16)		
I don't know how I could report an ADR to the relevant authorities	724	2.86 (1.30)	17.1% (124)	29.4% (213)	14.1% (102)	28.6% (207)	10.8% (78)		
Opinion regarding current and future role in pharmacovigilance									
Medical students can report ADRs during their clerkships	724	3.18 (1.02)	4.8% (35)	20.6% (149)	36.5% (264)	28.2% (204)	9.9% (72)		
Reporting known ADRs makes no significant contribution to the reporting system	724	2.24 (0.98)	20.7% (150)	50.7% (367)	15.1% (109)	11.3% (82)	2.2% (16)		
With my present knowledge, I am very well prepared to report any ADRs in my future practice	724	2.77 (1.02)	7.0% (51)	41.9% (303)	21.5% (156)	26.4% (191)	3.2% (23)		
I believe that doctors are one of the most important healthcare professionals to report ADRs	724	3.98 (0.75)	1.0% (7)	3.7% (27)	12.0% (87)	63.3% (458)	20.0% (145)		
I believe that pharmacists are one of the most important healthcare professionals to report ADRs	724	3.73 (0.92)	1.0% (7)	12.0% (87)	17.7% (128)	51.8% (375)	17.5% (127)		
I believe serious and unexpected reactions that are not fatal or life-threatening during clinical trials should not be reported	724	1.43 (0.65)	63.5% (460)	31.8% (230)	3.3% (24)	0.8% (6)	0.6% (4)		

educational approaches to pharmacotherapy education for undergraduate medical students.

In this study, students expressed a desire to be taught more about pharmacovigilance during their medical education and would prefer to learn in real-life practice. We urge (inter)national pharmacovigilance centres to collaborate with clinical pharmacology teachers to develop educational interventions that can be incorporated in the formal medical curriculum. One such easy-to-implement intervention is an ADR reporting assignment [12]. Further research is needed to design and evaluate new educational interventions to stimulate early clinical pharmacovigilance experiences for undergraduate medical students and to assess the effect of these new interventions. In this way, when junior doctors start to work in clinical practice, they will know what to do and where/what to report when they encounter an ADR.

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Contributorship Statement

All authors contributed to the conception and design of the work, drafting the work and revising it critically for important intellectual content. All authors provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Transparency Declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Supplement digital content 1 - baseline characteristics of participating students.

Table S2. Results of open questions regarding actions one would take If you suspect a patient to have an adverse drug reaction.

Table S3. Responses on open question: 'I know where to report an adverse drug reaction (in the Netherlands)'. Multiple answers possible.

Table S4. Responses on question: "I know which details are needed for a good ADR report. Multiple answers possible.